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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,521	03/17/2004	Daniel P. Wermeling	INT-002C1CP	5461

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EXAMINER	
YU, GINA C	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
05/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/803,521	WERMELING, DANIEL P.	
	Examiner	Art Unit	
	GINA C. YU	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-15,17,18,20 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15,17,18,20 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of response filed on March 25, 2009. Claims 11-15,17,18, 20 and 27-29 are pending.

Obviousness double patenting rejections as indicated in the previous Office action dated January 27, 2009. New rejections are made in view of further consideration, and the finality of the previous Office action is hereby withdrawn.

Terminal Disclaimer

The terminal disclaimer filed on March 25, 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Pat. No. 6610271 and U.S. Pat. Application 11/376979 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11, 13, 15, 18, 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over view of Knoester et al. (Br. J. Clin. Pharmacol., 2002) in view of Bechgaard (Pharm Dev. Technol., 1997) and Haslwanter (U.S. Pat. No. 5897858).

Knoester teaches pharmacokinetic and pharmacodynamic study of concentrated midazolam nasal spray. The reference teaches intranasal midazolam has been used as premedication and sedative agent to manage acute seizures. See p. 501, Introduction; instant claim 20 and 28. The reference indicates in the study subjects were administered single doses of 5 mg midazolam. The formulation comprises midazolam

hydrochloride in a mixture of water and propylene glycol. See p. 502, Midazolam formulation. Benzyl alcohol, which acts as an anesthesia, was added as an antimicrobial preservative. See p. 506, second column, first full paragraph; instant claims 13 and 15. The study shows midazolam was rapidly absorbed after intranasal administration, with a mean peak concentration of 71±25 ng/ml reached after 14 ±5 minutes. See p.504, Pharmacokinetics; instant claim 18. The reference also teaches the dose of intranasal midazolam for treating seizure is based on body weight; 0.2 mg/kg for children, 5 mg for adults under 50 kg, and 10 mg of midazolam for adults weighing more than 50 kg. The reference also teaches conventionally a relative large volume, 1-2 ml of 5 mg/ml midazolam composition were administered to adult patients, causing discomforts, and suggests that these advantages would be overcome by increasing the concentration of midazolam. See p. 501, first column, first and second full paragraph. Knoester teaches the study employed 2.5 mg of midazolam was administered in 0.9 ml spray in each nostril of the subjects.

Knoester fails to teach polyethylene glycol (PEG).

Bechgaard teaches solubilization of various benzodiazepines including midazolam for nasal administration. The reference teaches the solubility of drugs is critical for intranasal application because one clinical dose needs to be dissolved in a volume not exceeding about 300 micro liter for the administration. See p.293, first column, bridging paragraph. The reference teaches polyethyleneglycol increases the solubility of benzodiazepines due to its pronounced lipophilicity. Table 2 shows a superior solubility of midazolam in PEG 200 in among other benzodiazepines (140 mg/ml). Since the

reference teaches it is possible to dissolve midazolam 140 mg/mL, and teaches the clinical dosage for midazolam is 5 mg, formulating a 25 mg/mL midazolam solution using PEG would have been within the skill of the art. See instant claims 28 and 29.

Haslwanter teaches an aqueous nasal spray formulation which exhibits increased retention in the nasal cavity. The reference teaches using up to about 15 % by weight/volume of PEG. See col. 3, line 56 – col. 4, line 34. The reference also teaches that sterile water is used to prevent microbial contamination. See col. 2, lines 55-67. The reference teaches PEG 200 and 400 are clear viscous liquids at room temperatures. Since both PEG 200 and 400 are low molecular weight glycol polymers with similar physical properties well known in intranasal spray art, substituting one for the other depending on the desired viscosity would have been obvious to a skilled artisan. See instant claim 27.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the teachings of Knoester by incorporating polyethylene glycol as the solvent for midazolam as motivated by the combined teachings of Knoester, Bechgaard, and Haslwanter because 1) Knoester suggests increasing the concentration of midazolam to reduce the amount of the spray fluid necessary to deliver the effective dosage of the drug; 2) Bechgaard teaches polyethylene glycol dissolves up to 140 mg/ml of midazolam; and 3) Haslwanter teaches the range of the amount of polyethylene glycol which may be successfully used for an intranasal spray formulation. Discovering an optimum amount of polyethylene glycol as applicant has done would have been obvious in view of the teachings of Bechgaard and Haslwanter.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, Knoester suggests more concentrated midazolam spray solutions are more advantageous and teaches 0.9 ml solution containing 2.5 mg of midazolam; and 2) Bechgaard teaches the solubility of polyethylene glycol 200 which dissolves 140 mg/ml of the drug; and 3) Haslwanter teaches using up to 10 % by weight/volume of polyethylene glycols in nasal spray increases retention in the nasal cavity. Since the references teach the required amount of polyethylene glycol for bioavailability in the nasal cavity and the solubility of the drug in the glycol, discovering an optimal amount of polyethylene glycol as an effective solvent and carrier for midazolam by routine experimentations would have been obvious to one of ordinary skill in the art.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over view of Knoester, Bechgaard, Haslwanter as applied to claims 11, 13, 15, 18, 27-29 as above, and further in view of Mukae et al. (US 5789375).

Although Knoester teaches using propylene glycol in the intranasal solution, the reference fails to teach the amount of propylene glycol as required in the instant invention.

Mukae teaches using up to 70 % by volume of glycols to make a nasal composition which is low in irritation and highly absorbed through the nasal mucous membrane. See col. 3, line 40 – col. 4, line 37. The reference teaches that propylene glycol is particularly preferable since it's been practically used as an additive to pharmaceuticals. The reference also teaches that the upper ratio in which alcohols are contained in the composition is determined depending on the kinds of alcohol used, combinations of the alcohols, the effect or advantage to be derived from alcohols, etc. See col. 4, lines 13 – 21. Adding thickeners or gelling agents, such as polyethylene glycol, for enhancing the retentivity of a medicine on the nasal mucosae is also taught. See col. 5, lines 17 – 33.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the nasal composition of the combined references by incorporating the glycols-based vehicle as motivated by Mukae, because the latter teaches using propylene glycol based vehicle for low irritation and high absorption of active drugs. Given the general teaching in Mukae that the amounts of alcohol vary depending on the types of the drugs and other factors, the skilled artisan would have discovered the optimum amount of the propylene glycol suitable for midazolam by routine experimentations. The skilled artisan would have had a reasonable expectation of successfully producing a stable propylene glycol based nasal composition in admixture with polyethylene glycol because Mukae teaches that the latter is suitable thickener for enhancing the retentivity of a medicine on the nasal mucosae.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over view of Knoester, Bechgaard, Haslwanter as applied to claims 11, 13, 15, 18, 27-29 as above, and further in view of Craig et al. (US 5554639).

The combined references fail to teach a preservative-free composition.

Craig teaches that a sterile, preservative-free nasal solution is preferred. See col. 3, lines 1 –4. Example formulations show an aqueous sterile composition comprising sodium saccharin and an active ingredient. See Examples 14-17. Using polyethylene glycol 400 for nasal solution is taught in col. 2, lines 53-57. See instant claim 28.

It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the nasal composition of the combined references to make a preservative-free nasal spray composition as motivated by Craig because it would be more desirable to use sterile formulation without preservatives. The skilled artisan would have had a reasonable expectation of successfully producing a preservative-free, sterile nasal formulation containing midazolam.

Claims 17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over view of Knoester, Bechgaard, Haslwanter as applied to claims 11, 13, 15, 18, 27-29 as above, and further in view of Fisgin (J. Child Neurol., 2000).

The combined references do not specifically teach whether the midazolam intranasal administration achieves sedation within 5 minutes as required in the instant claim.

Fisgin teaches nasal midazolam effects on childhood acute seizures. In the study, midazolam (5 mg/ml) intranasal was administered in a 0.2 mg/kg dose to children aged from 2 months to 14 years. The reference reports that the seizures of 3 patients were terminated within 1 minute, and of 7 patients within 2-5 minutes. See abstract.

Since Fisgin teaches conventional intranasal administration of midazolam already achieved terminating acute seizures of children within 5 minutes, it would have been obvious to one of ordinary skill in the art that a nasal spray with enhanced solubility of the drug and nasal retention of the combined references would achieve even a better result.

Response to Arguments

Applicant's arguments with respect to claim 11-15, 17, 18, 20 and 27-29 have been considered but are moot in view of the new ground(s) of rejection.

In the declaration filed on November 7, 2008, applicant asserts the amount of polyethylene glycol and propylene glycol is critical in achieving maximum plasma concentration of midazolam. However, the argument is not commensurate with the scope of the claims because Knoester already teaches midazolam intranasal compositions for sedation comprising propylene glycol which achieves maximum plasma concentration within about 10 minutes, and the present claims do not limit the amount of propylene glycol. Nor is the scope of the claim limited to only two glycols of the present claims. The claim is open to include any other components other than the unspecified amount of propylene glycol. Furthermore, the motivation to incorporate polyethylene glycol to a midazolam intranasal spray is taught in Bechgaard, as

discussed above. Thus, examiner views the obviousness rejections as discussed above are proper in this case.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINA C. YU whose telephone number is (571)272-8605. The examiner can normally be reached on Monday through Friday, from 9:00AM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gina C. Yu/
Primary Examiner, Art Unit 1611